



Second meeting of the CIOMS Working Group on Severe Cutaneous Adverse Reactions of Drugs (SCARs)

13 April 2021

Meeting Minutes

Members

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CIOMS staff and management

Catherine Bates, Kateriina Rannula, Hervé le Louët and Lembit Rägo

Regrets

Matt Doogue (IUPHAR/University of Otago/Christchurch), Sylvia Lesperance (Novartis)*, Sarah Schlieff (Bayer) and Sabine Straus (MEB)

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**New member

Introduction

- Lembit welcomed the Working Group (WG) on Severe Cutaneous Adverse Reactions of Drugs (SCAR) and introduced Catherine as the new Medical Writer who will be supporting the WG going forward.
- He stated that the objectives of today's meeting are
 1. Have a clear vision of how to merge the two tables of content (TOCs) into one document
 2. Agree this process
 3. Discuss how to reach the next stage, i.e. drafting the guidelines

Hervé suggested that the purpose of this call was more to review the work conducted by the two subgroups to date rather than to achieve concrete progress. He added that the two options were not that different so merging them should be an easy task. The next step is to start thinking about who would draft the first version of the guidelines.



Subgroup 1 presentation

Melissa presented on behalf of the group

- They debated what the title of the group should be namely, SCAR, but that other skin reactions should be included in the document as well. So, the working group name is SCAR and other drug-induced skin injuries was the terminology that was chosen. Melissa then proceeded to go through each chapter
- Regarding Chapter 7 on drug safety, while assessing causality is important, the chapter would not be complete unless risk was communicated effectively. The question of integrating communications throughout the drug life cycle was raised. The group also talked about risk/benefit of different populations e.g. cancer or HIV patients, risk/benefit might be different for acne patients.
- Regarding appendices: the group proposed having a mock case report, similar to the drug-induced liver injury (DILI) guidelines as well as examples of the narrative and graphical profile.

Melissa asked for comments on her summary. Leslie said it was comprehensive and that she did not have anything to add.

Comments on subgroup 1 presentation

Neil pointed out that the main difference between the two groups is the inclusion of drug-induced skin injury (DISI). Maybe the group should clarify this at the beginning, but focus on SCAR as this is what the remit is. In response to this, Melissa remarked that the group had initially included it in the appendices and then put it back in the main document. So another option would be to mention it in the beginning and covered in the appendix with short descriptions of what to consider. This is where the mechanistic vs phenotyping approach would matter and how they would be included.

Hervé raised the point about an important distinction to make between severity and seriousness. The group is talking about seriousness, not severity.

Subgroup 2 presentation

Neil presented for subgroup 2 and began by saying there was quite a lot of overlap with group 1, as expected.

Regarding the order, the science is relevant, but he wished to make a plea: to make diagnosis come first, then determine causality. Then, there is the reporting and all the other things that come into play, but that is a whole different story.

Include section on the role of the dermatologist because dermatologists will not be making these decisions most of the time. So, scientists conducting clinical development know what to look for e.g. in terms of safety.



In terms of targeted therapies, these bring about a whole set of adverse events, but we are also seeing a different approach because if the treatment is stopped, the patient could die. Neil posited that this is a great opportunity (for CIOMS) to take leadership in that area.

Clinical care: Especially for conditions such as toxic epidermal necrolysis (TEN), the literature is conflicted about clinical care except for a few things which are not drug-induced like in the case of amnion for the eyes that help you from becoming blind. But the role of drug therapy for TEN is.

The group also discussed how to present or analyze the material. Neil commented that he has been using the graphic approach for years; that it is the only way to sort out complex stories and it would be useful to see data in CIOMS reports included in a graph.

Comments on subgroup 2 presentation

Hervé asked Neil to expand on the idea that SCAR should not be considered differently from DILI. Neil came back on his explanation, saying that he was referring to DISI, not DILI.

Alex reiterated Neil's comment about keeping DILI as a differential diagnosis and not get into the details of specific DISI's, but instead, focus on SCAR. Neil concurred and highlighted that DISI includes so many conditions that the group should not go into them, beyond providing a definition.

Violeta raised a question about DILI. If one is talking about an initial presentation of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) for instance, where you observe aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) and you need to differentiate from a pure DILI event, the management might defer in terms of when to introduce steroids. This might not be the case for DILI, so should the group provide some guidance regarding the diagnosis or the initial manifestations in order to differentiate between a "pure" DILI event and a DRESS case?

Hervé interjected by saying that there was extensive discussion by the group to know if DRESS was a DILI with a cutaneous syndrome or the opposite. Ultimately, what was decided by the group was that it was easier to define it cutaneously because we have the index state and know when it began. With the DILI approach, one cannot have the index state which creates problems when it comes to causality assessment.

Hervé pointed out that there is a clear syndromic definition for DRESS. So, one needs DILI, of course, but this represents only 80% of cases. It is not always present. The group needs to make a decision about this as prescribing corticosteroids on a DRESS generally is a treatment for cutaneous syndromes. However, it could also lead to flare-ups so the liver must be monitored closely when prescribing corticosteroids. Unfortunately, we do not have a solution, but it is important to be aware of this.

Neil thanked Hervé for this comment because it also addresses the overlaps which can be challenging and confusing. It is a good idea to clarify a situation when there is an overlap. Is it purely a DILI or DRESS or both?



Chia-Yu was asked for his thoughts on the matter. He began by saying that he co-authored a paper three years ago about liver injury in DRESS and suggested that liver injury is a component of DRESS. He believes the group can include liver injury as part of DRESS, but maybe not use the term DILI in the section on DRESS.

Neil agreed that it is important to cover this and that the group should also think about the dynamics of the therapy. In DRESS, one will often see a secondary flare-up, which might not be life-threatening, but can be expected even if the drug has been stopped. There is definitely a story around the liver.

Discussion

Terminology

Melissa suggested to possibly include a history of terminology in the introductory chapter. Historically, erythema multiforme (EM) is a term that gets mixed in and it might be useful to put it into context as the terminology has evolved a lot over time. Now, with a more mechanistic understanding, it has become clearer.

Neil agreed with this point of view. He mentioned that when he was doing the original SCAR study, he had a place for people who did not fit Stevens-Johnson syndrome (SJS) at the time. And then you have recurrent reactive infectious mucocutaneous eruption (RIME), mycoplasma pneumoniae-induced rash and mucositis (MIRM) and Fuchs disease and there are a lot of different terms for this group of diseases, which he now calls SJS Type 1.

He refers to SJS-TEN as SJS Type 2. The point is not to come up with new terms or new words, but rather to bring clarification to existing terminology. Neil then mentioned the case of a young boy with target lesions, which would not really fit, but would fit with one of those other diseases that have four or five different names. Neil stated that new names are not helping. One can keep the old ones, but make them a little simpler. It gives a better sense of where things belong and what the prognosis will be.

Neil offered to put the above in a separate document for the group. He also mentioned a paper published in Japan in 2011 in the allergy literature looking at SJS Type 1 which could be a useful reference.

Ariel agreed that this type of history would be useful for different functions represented by the group, namely: clinicians, regulators and industry, so the group can focus on the terms it will be using going forward. Ariel also reminded the group that it would be important to state the objective of this guidance document so the audience understands what the group is doing, namely providing standards of diagnosis that will be used, not only by clinicians, but industry and regulators as well. So there is a consensus on the minimum criteria to meet in order to establish that e.g. it is a case of SJS. This would have to be laid out in the introduction.

Skin of color and photos

Neil further commented that there are two groups: one pediatric which need its own focus and the other is, skin of color. There is a lot going on in this regard and is a hot topic right now.



With regard to confounding aspects, varicella sometimes looks like TEN and at other times, TEN looks like varicella in very dark skin. The group should address the skin of color issue.

Filippa asked if it was possible to link to atlases as discussions have become so theoretical. It would be nice to include photos, but the problem is people will “see what they know” and often time, the photos are not good quality and are out of focus. However, it might be helpful to insert a few pictures anyway so readers get a good understanding of the issue.

Hervé suggested that as one is publishing more and more digitally, maybe the group could insert links to reliable databases with good pictures. Maybe also include links in the hard copy of the document so as not to comprise the quality of the photo. However, it would be a big job to select the best photos. Neil agreed with the view that it would be a lot of work to choose the best photos. However, when describing the skin of color issues, it would be particularly useful to have just a few photos so readers know what the authors are talking about.

Hervé suggested that photos can sometimes be misleading.

Filippa agreed with the idea to provide links to some atlases. The problem then is to ensure the links are kept up-to-date, as Hervé observed. Filippa then suggested including links to other societies, e.g European Dermatology Forum and informing them that CIOMS is conducting this work so they could take up this topic as well.

Lembit supported the idea of including links to other sources as the more doable approach and welcomed the initiative regarding the European Dermatology Forum’s promoting the CIOMS paper. Filippa added that it would take a long time for this to happen, but a good start would be to alert them. She went to say that one or two photos would be beneficial in helping the reader, particularly in terms of the skin of color discussion.

Melissa asked if there might be a possibility of receiving photos as a donation from one of these dermatology bodies. What would erythema in skin type 1 to 2 look like vs the other end of the spectrum and just one photo of each could be extremely informative.

It would also be an opportunity to correct the terminology for physical descriptions. When one looks at post-marketing reports, sometimes the descriptions do not fit, so having that in the CIOMS guidelines is a good way of providing an appropriate clinical description. It would also be supportive of the diagnosis for case selection.

Lembit continued by stating that photos are helpful if they are good quality, but if the group could identify a few bodies that could help CIOMS in this regard and for example in exchange, give recognition to their work. CIOMS would have to be very clear as to what examples it wants to present and explore potential partners in this effort.



Alex alerted the group to the risks of underdiagnosis or overdiagnosis in displaying photos and if this CIOMS publication is to be used as a reference, we do not want it to lead to misdiagnoses of SCAR because the symptoms do not look like the picture that is referenced.

Leslie expressed her view about the importance of pictures for documenting case reports. Guidance in this regard is often reinforced in the context of clinical trials. However, as it may not be as common practice in post-marketing situations, it would be useful to remind health care professionals of the relevance of pictures to support an appropriate diagnosis of any potential SCARs.

Chia-Yu was in agreement about the risks of including photos as different eyes are used to see the same things. He also mentioned that in the RegiSCAR Group, there is a website with some good quality photos on it.

Violeta flagged that another issue could be the timing, e.g if it is something that is seen at the beginning of the reaction, the appearance will be completely different from a typical textbook illustration.

Lembit remarked that it is a complex issue, but that it should nevertheless be described in the CIOMS document, including the limitations of providing photos, what they can and cannot show. It would be useful to have photos to illustrate examples in skin of color and so, further thinking is required about how to present this case and which would be the reliable sources to be included. The group would be able to reach a consensus on how to solve this.

Case report forms

In response to Neil's presentation on subgroup 2, Alex noted that there was no case report form. Subgroup 1 thought they should have something as a guidance and wanted to make sure they did not miss anything. Neil responded that they do have case report forms from CIOMS. It is meant to be a generic one that anybody can use. Neil then asked Alex if what he had in mind was to have a unique form for this. To which, Alex replied yes. It is actually a case report form and narrative specific for SCAR, the same as what the group did on DILI.

Hervé intervened, saying that the problem with case report forms is that one needs to share two different situations i.e. the clinical trial where you have all the information you need and the current pharmacovigilance practice. RegiSCAR created a case report form which was extremely complicated to fill in. It can be a tool and a help, but shouldn't limit the reporting because if people see the long list we need to make a proper diagnosis, they would not bother. So, we should mention that it is the maximum that can be done, but a hierarchy should be provided to rank the different criteria. This was discussed at length in the DILI group.

Lembit confirmed that this was discussed in the DILI group, but that in the end, there was a lot of support to have something specific for DILI because especially in clinical trials, it helps to have a



uniform approach to document it. But in a clinical setting, having a more uniformed approach would be helpful.

Neil expressed concern about the current free space form for CIOMS in clinical trials, one can pretty much write what one wants and whenever one has tried to conduct studies internationally, with boxes that one fills in and check marks, it seems like it is about 100 pages.

Melissa said there could be a compromise, that it would help to have some kind of standardization of what are the useful data points. It can be tedious to go through them because if you do not know whether it is acute generalised exanthematous pustulosis (AGEP) or SJS, you do not know which form to use. This can be a potential challenge. Some kind of guidance would be useful to help fill up the free space. Pictures are invaluable for the trained eye and could be more informative than a long narrative assuming they are being looked at by a trained eye. She would like the guidelines to address all of this, but how they fit it in will be a challenge. Compared to DILI, all this morphology and visual aspects is hard to capture and having it meet the needs of the different audiences.

David agreed that the form has limitations and cannot include everything because it would be too long. It would not be applicable to all cases. But at least, garner the minimal information that comes up in most scenarios.

Ariel recommended to maybe adapt the general form and then add components to it. He sees it as just one form for all SCAR and then include e.g. phenotypic manifestations, histology and leave a blank there so readers understand this is what is needed to establish a diagnosis. He does not believe a separate form is needed for each type of SCAR, but rather, the group could produce a single form and then from each component, the user will be able to provide information to establish a diagnosis.

Neil's view was that if there is a link that CIOMS keeps up to date, one could use the blank form, but if one wanted to go to something that CIOMS has and that might be specific to conditions, he was not sure how dynamic it could be.

Based on Alex's experience as part of a clinical program, the form was used to trigger additional data collection. So every time a patient presented a skin reaction, questions were asked about mucosal involvement and others, and if any of the answers were yes, additional data collection was triggered, e.g. photos or calling a dermatologist. Maybe, as Melissa mentioned, the guidelines could provide a minimum set of endpoints that need to be collected as a guide for clinicians who are seeing patients. Lembit explained that this task could be left to the two subgroup leads with support from a few members because the group would not be able to do this now.



Next steps

Lembit asked the group if they had any thoughts on how to proceed with the guidelines. His view was that those who have contributed to the subgroups are in the best place to work on combining the documents. Then a consolidated version could be circulated for comment to the whole group. The next question is how to mete out the drafting, which depends on how many chapters the group expects to include.

Lembit's perspective was that a way forward could be that the WG is divided into three subgroups, with each drafting three or four chapters.

Neil asked if CIOMS would facilitate the connections or if members should contact each other directly. Lembit replied that the CIOMS support person would be available to help the subgroups in this regard. There would be a meeting of the whole group at some point when the three subgroups could come together and share progress to date on their respective drafts.

Reconciling the two TOCs

Priya recognized that the TOCs could not be merged at the time of the meeting, but maybe the two documents could be displayed side by side on the screen and compared to understand differences and get some direction from the group which would be useful for the person who volunteers to do the drafting. It seems one document is more clinically-oriented while the other is more focused on the reader.

Priya proposed to maybe use the structure from one and the detail from the other. She asked if the guidelines will only focus on SCAR or on other drug-induced skin reactions as well. Also, on the subject of communications, Priya suggested, instead of having a dedicated chapter on communications, the group could show how communications could be integrated into each of the various stages such as drug development, clinical use of the medicine, regulatory. She followed up by saying that this would depend on how the other subgroup feels about this as they viewed it as a separate topic.

The group believed there might be some principles they could discuss in this meeting to help the person who will be drafting the paper.

Lembit stated that there would not be just one person who does the drafting, but the two subgroup leads could take the process forward given that they know the background.

Hervé felt that it was not only a problem of merging, but there are real differences between the two which require further discussion before they can be merged and as Priya stated, they represent two different philosophies even if the titles are more or less the same.



Defining the scope

Priya provided the following as next steps:

1. Define the scope in terms of which skin reactions to cover;
2. Determine whether the guidelines are mainly intended for clinicians or assessors or everybody (this will dictate the structure and the style);
3. Decide if the communications aspects are an integrated function or a separate entity? Priya suggested it is both.

In response, Neil agreed that the scope should be SCAR. DISI should be mentioned, but not delved into in great detail. Furthermore, he put forward the suggestion to include a stand-alone section for clinicians, one for reporting and also asked how to decide which perspective to adopt, e.g. a clinician or a regulator. How was this addressed in the DILI guidelines? Lembit explained that CIOMS publications are aimed at the organization's main stakeholders, namely industry, regulatory and academics.

Hervé referred to a comment in the chat by Melissa and which was about describing the context of DISI. He felt it was important to discuss this with other group members. Lembit added that there was support from other members for this point.

According to Chia-Yu, the main difference between the two groups is whether DISI and SCAR are treated together. One of the members said the focus should be more on SCAR because DISI includes many different types of drug reactions. He believes the main types of drug reactions should be covered because for many clinical trials, with new drugs, the key is to understand how to differentiate between SCAR and common types of reactions. These could be presented in a supplementary table but DISI should be the starting point and be described in the introduction and then move on to the more specific terms of SCARS and mention how to distinguish between the two. If this information were laid out in a table, the group would not need to include too much detail on each of the reactions. When one talks about new agents, e.g. cancer immunotherapies, DISI must be mentioned again otherwise the document would not be complete.

An approach based on the different stages of the product life cycle

Building on Chia-Yu's position, Priya pointed out that the scope is not only what is included, but also what is excluded and found this a convincing position. Furthermore, she posited that one could imagine the whole pharmacovigilance chain whereas regulators often leave out the use of the product. The risk-benefit life cycle management has everything in it except the use of the product which is not in the cycle. If the whole process is thought of as a cycle, then each of the stages that the product goes through from development to approval to use and then being further managed by regulators, could be a way to structure the paper. And then, the diagnosis and data gathering come together naturally in the clinical setting, with other aspects such as signal generation comes next. So, maybe that could be a natural way to look at it.

Comments on Priya's proposal:

Filippa had a comment on the process for the document. Both are valuable. Her recommendation would not be to merge them at this point, but rather to write out some of the



sections in both papers so the group can see where the controversial points are in each. This would possibly simplify the process and also help to address any controversies.

Forming a “merging the TOCs” subgroup

The group thought this was a good suggestion and Lembit then followed up by asking the two subgroup leads to begin by highlighting the similarities and if the “merging the TOCs” subgroup cannot resolve any differences on its own, it could bring them to the attention of the whole group who could discuss and reach a consensus.

Melissa asked for clarification as her understanding is that the two groups will be working separately and then come together before a larger group meeting. Lembit responded by saying that the groups would not work separately, but instead, the two subgroup leads would work together with some other working group members. If there are some points that require input from the whole group, the latter can be convened accordingly.

Neil suggested that an email go out to the working group asking members what role they would like to have or if they do not wish to participate, they might nevertheless, have some comments they would like to share. Lembit asked for volunteers to help Melissa and Neil:

1. Alex
2. Filippa
3. Chia-Yu
4. Ariel
5. Haur Yueh Lee
6. Siew Eng Choon

Should any other working group members be interested in joining this new subgroup, they are welcome and should let CIOMS/subgroup leads know.

CIOMS will support the new subgroup to identify availabilities for a meeting and then find a date for a full working group meeting at a later stage.

Concluding remarks

Priya raised a question about vaccines and whether the group had considered them, e.g. SCAR and vaccines. Neil’s view was that one does see things from COVID itself. Probably, the most common cause of multiform erythema now is COVID. Vaccines are a very different world.

Roni mentioned a new study she received by Professor Elizabeth Philips on a case of AGEP in a COVID patient. There is also a paper which was just published by an Italian group on cutaneous effects of the Pfizer vaccine. She will share both with the group by email.

Referring to the idea of covering vaccines in the scope of the guidelines, Lembit said it might require further thought to see how it could be addressed. It could be helpful even if it is short.



Neil suggested writing a disclaimer as there are many technologies that cause cutaneous reactions besides drugs. Maybe a summary statement would suffice. It would not require a lot of detail, but people should be reporting.

Hervé's recommendation was that the group should not focus on COVID because there could be a different pandemic tomorrow. Rather, what is important is the context and if something could happen in the COVID context like it happened with HIV which modified the safety profile of many drugs. He does not believe a dedicated chapter on COVID is required.

Lembit offered that it would be a good idea to include some insights on biologicals in the guidelines. He closed the meeting by saying the group had a plan which could be taken forward and thanked the members for their time and participation.

Who?	What?
Catherine	Send email to the WG including: <ol style="list-style-type: none"> 1. Draft minutes 2. List names of merging subgroup as agreed in the meeting 3. Ask if any other WG members are interested in joining this subgroup and if not, whether they have any additional comments
Roni	Share two papers with WG (done)
Neil	Overview of terminology e.g. SJS Type 1 vs SJS Type 2 for the group